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RESPONSE AFTER FINAL REJECTION
EXPEDITED PROCEDURE
EXAMINING GROUP 1640

PATENT
Attorney Docket No. 02481.1597

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
Johann ERTL et al.)
Application No.: 09/099,307) Group Art Unit: 1646
Filed: June 18, 1998) Examiner: C. SAOUD
For: NOVEL INSULIN DERIVATIVES)
HAVING A RAPID ONSET OF ACTION)

#15
/JPP
(N.E.)

Assistant Commissioner for Patents
Washington, D.C. 20231

REQUEST FOR RECONSIDERATION AFTER FINAL REJECTION

Sir:

In response to the Final Rejection mailed February 28, 2000, Applicants respectfully request reconsideration and withdrawal of the Final Rejection in view of the following remarks and those of the previous response. The shortened statutory period for response to the Final Rejection is extended by three months, to August 28, 2000, by the Petition for Extension of Time and fee filed herewith. Claims 1-36, 41-58, and 61-67 are pending in this application, all but claims 1 and 28 having been withdrawn by the Examiner as directed to non-elected species.

In the Final Rejection, the Office maintains the rejection of claims 1 and 28 as unpatentable under 35 U.S.C. § 103(a) over Brange (U.S. Patent No. 5,597,796; "Brange") in view of Markussen *et al.* (WO 92/00321) and Brange *et al.* (WO 89/10937; "Brange *et al.*").

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Applicants respectfully traverse this rejection and submit that the invention of claims 1 and 28 would not have been obvious to one of ordinary skill in the art at the time of the present invention in view of the combination of cited references.

I. *Brange Teaches Away from Introduction of a Positive Charge in an Insulin Analog.*

As discussed in Applicants' response of December 2, 1999, Brange teaches insulin analogs that remain in monomeric form in relatively concentrated compositions due to substitutions at defined residues within the A- and B-chains. The analogs can remain in monomeric form because the substitutions render the insulin more negatively charged by replacing naturally-occurring amino acids with glutamic acid or aspartic acid. Because of their increased negative charge, and thus their ability to remain in monomeric form at high concentrations, the analogs disclosed by Brange show a rapid onset of activity. Brange indicates that B3 is a particularly good position for substitution with glutamic acid or aspartic acid. Further, Brange exemplifies insulin analogs having the asparagine at B3 substituted with glutamic acid. Brange does not disclose or suggest placing a positively charged amino acid at position B3.¹

The Office asserts that claims 1 and 28 are rendered obvious over Brange in view of Markussen *et al.* and Brange *et al.* More specifically, the Office asserts that Brange teaches insulin analogs with substitutions at B29 and B3, but not substituted at B3 with a positively charged amino acid. The Office then asserts that the deficiency of Brange (no positive residue at

¹ This fact is apparently accepted by the Office at paragraph 7, page 3, of the Final Rejection ("Brange ('796) does not teach substitution of B3 with a basic amino acid.")

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B3) is overcome by combining Markussen *et al.* (for the teaching human insulin substituted at B1-B6 with a positively charged residue) with Brange. The Office states that motivation to combine the substitution of a negatively charged residue at B29 (Brange) with a substitution of a positively charged residue at B3 (Markussen *et al.*) comes from Brange *et al.*, which teaches that multiple substitutions in insulin are desirable to stabilize the insulin and prolong its activity.

Applicants respectfully reassert the arguments presented in their response filed December 2, 1999, and submit that the Office has improperly combined the cited references and thus has failed to set forth a proper *prima facie* case of obviousness. More specifically, Applicants respectfully submit that the Office has improperly combined Brange with Markussen *et al.* and Brange *et al.* because Brange teaches away from insulin analogs with positively charged residues at position B3.

In the Final Rejection, the Office states that Applicants' arguments were not persuasive because Brange does not require substitution at B3 with a negative amino acid in order to achieve the desired activity. Final Rejection at paragraph 7. However, the issue is not whether Brange requires a negative charge at B3, but whether Brange, taken as a whole, would have discouraged one of ordinary skill in the art at the time of the present invention from creating an insulin analog having a positive charge at position B3. As discussed above and in the previous response by Applicants, and as is evident from the disclosure of Brange, Brange is concerned solely with minimizing association (multimerization) of insulin monomers in highly concentrated compositions so that insulin will have a rapid onset of action when administered. According to Brange, association is minimized by introducing negatively charged amino acids into the insulin

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amino acid sequence, resulting in an insulin analog having a greater negative charge than the wild-type insulin. Residue B3 is specifically cited in Brange as a residue at which substitution with a negative charge should be placed. Brange at column 9, lines 1-5.

Thus, introduction of a positively charged amino acid at position B3, as suggested by the Office, would be inconsistent with, and contrary to, the disclosure of Brange because such a substitution would not result in a more negatively charged insulin. Thus, Brange teaches away from such a substitution. Accordingly, there would have been no motivation to modify Brange as suggested by the Office. Thus, the Office has failed to set forth a *prima facie* case of obviousness. For at least this reason, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 and 28 under 35 U.S.C. § 103(a) over Brange in view of Markussen *et al.* and Brange *et al.*

II. *Modification of Brange as Suggested by the Office Would Change the Principle of Operation of Brange.*

The Office asserts that one of ordinary skill in the art would have been motivated to combine Markussen *et al.* with Brange "because the Markussen modification would increase the potential for aggregation which would be compensated by the modification of Brange ('796) ... in order to receive the combined benefit as taught by Brange *et al.*" Final Rejection at paragraph 7, page 4. However, as discussed above, Brange is directed to insulin analogs that remain in monomeric form at high concentrations. Maintenance of the monomeric form at high concentrations permits one to obtain a rapidly acting insulin (*see* Brange at column 4, lines 19-23, for example). Thus, the principle of operation of Brange is rapid action of insulin analogs

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through maintenance of monomeric insulin, even at high concentrations. If, as the Office suggests, introduction of a positive charge at B3 would increase the potential for aggregation and prolong its action (as taught by Markussen *et al.*), then such a modification would change the principal of operation of the insulin analogs of Brange. If a proposed modification of a prior art teaching would change the principle of operation of that prior art teaching, then such a modification is improper and fails to have rendered a claim at issue *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). *See also* MPEP § 2143.01.

Because modifying Brange with Markussen *et al.* would have changed the principle of operation of Brange, the two teachings cannot be combined to arrive at the presently claimed analogs of claims 1 and 28. Thus, the Office has failed to set forth a *prima facie* case of obviousness. For at least this reason, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 and 28 under 35 U.S.C. § 103(a) over Brange in view of Markussen *et al.* and Brange *et al.*

III. *Markussen Teaches Away from Introduction of a Negative Charge at Position 29 in the B Chain of an Insulin Analog.*

The Office has applied a combination of Brange, Markussen *et al.*, and Brange *et al.* against claims 1 and 28 of the present application. Although the Office has rejected claims 1 and 28 under 35 U.S.C. § 103(a), asserting that it would have been obvious to modify Brange with Markussen *et al.*, in view of Brange *et al.*, in an effort to expedite allowance of this application, Applicants will show that, even if the Office were to assert that it would have been obvious to modify Markussen *et al.* with Brange, in view of Brange *et al.*, claims 1 and 28 would be

patentable because such a combination would be improper, and thus, such a rejection would fail to satisfy the requirements for a proper *prima facie* case of obviousness. More specifically, Applicants respectfully submit that such a combination would be improper because Markussen *et al.* teaches away from insulin analogs having negatively charged substitutions in the B chain, particularly at position B29.

Markussen *et al.* teaches human insulin analogs with at least one of amino acids B1-B6 being replaced with a positively charged residue (*i.e.*, Lys or Arg). The insulin analogs have prolonged insulin action. Markussen *et al.*, Abstract; page 1, line 25, through page 2, line 2; and page 3, lines 1-21, for example. The insulin analogs show lower solubility than naturally occurring insulin. Markussen *et al.*, page 4, lines 4-7 and 22-26. Preparation of the insulin analogs relies on the presence of a Lys at position B29. Markussen *et al.*, page 6, line 30, through page 8, line 2. In comparison to wild-type human insulin, all of the exemplary analogs have increased positive charges at pH 7. Markussen *et al.*, page 9, lines 12-33; and page 11, Table 1.

The teaching of Markussen *et al.* that insulin analogs with prolonged activity should have a more positive charge than wild-type insulin would have discouraged one of ordinary skill in the art from introducing a negative charge in the insulin B chain. Introduction of a negatively charged residue in the B chain would be inconsistent with, and contrary to, the general disclosure of Markussen *et al.* because such a substitution would not result in a more positively charged insulin. In addition to this general discouragement, because Markussen *et al.* teaches that a lysine at position B29 is important for preparation of insulin analogs, Markussen *et al.* would

have specifically discouraged one of ordinary skill in the art from substituting a negatively charged residue for the lysine at B29.

Thus, one of ordinary skill in the art would not have found a motivation to modify Markussen *et al.* with Brange, in view of Brange *et al.*, to arrive at present claims 1 and 28. Accordingly, the combination of Markussen *et al.* with Brange, in view of Brange *et al.*, would fail to satisfy the requirements for a proper *prima facie* case of obviousness.

IV. *There Would Have Been No Reasonable Expectation of Success.*

Even assuming that one of ordinary skill in the art at the time of the present invention would have been motivated to combine Markussen *et al.* and Brange, and further was not concerned with changing the principle of operation of Brange (assumptions with which Applicants do not agree), there would have been no reasonable expectation of success in achieving the monomeric insulin composition of Brange.

Brange teaches that insulin analogs should have a more negative charge at neutral pH than wild-type insulin in order to provide a more rapid onset of action than wild-type insulin. As the Office recognizes, this, apparently, is the case whether a negatively charged residue or a neutral residue is present at position B3. However, Brange does not disclose or suggest what effect(s) a positively charged residue at position B3 would have on maintenance of the monomeric form of insulin. As discussed above, taken as a whole, Brange teaches that introduction of positively charged residues would be detrimental to achieving his analogs. This is especially true at position B3 (*see* Brange, column 9, lines 1-5).

The Office asserts that one of ordinary skill in the art would have expected the tendency to aggregate resulting from the Markussen *et al.* modification to be compensated for by the modification of Brange. Final Rejection at paragraph 7, page 4. Applicants respectfully submit that a person of ordinary skill in the art at the time of the present invention would have had no reasonable expectation of success if he were to have introduced a positively charged residue at position B3 in the insulin analog of Brange. More specifically, one of ordinary skill in the art would not reasonably have expected that the modifications of Brange would compensate for a positively charged residue at position B3, as asserted by the Office. Indeed, it is equally likely that one of ordinary skill in the art would have believed that introduction of a positively charged residue at position B3 would completely overcome the effects of the negatively charged residue(s) introduced by Brange, or have no effect on maintenance of a monomeric insulin whatsoever. Brange, Markussen *et al.*, and Brange *et al.* simply do not provide a reasonable expectation of success in achieving an insulin analog that maintains its monomeric form at high concentrations if the analog comprises a positively charged residue at position B3. In order for the Office to set forth a proper *prima facie* case of obviousness, a person of ordinary skill in the art must have had a reasonable expectation of success in achieving the claimed invention if the prior art were to have been modified as suggested by the Office. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). *See also* MPEP § 2142.

Because one of ordinary skill in the art at the time of the present invention would not have had a reasonable expectation of success in achieving an insulin analog that maintains its monomeric state at high concentrations, the combination of Brange, Markussen *et al.*, and Brange *et al.* fails to have rendered present claims 1 and 28 obvious. For at least this reason,

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 and 28 under 35 U.S.C. § 103(a) over Brange in view of Markussen *et al.* and Brange *et al.*

V. *Conclusion.*

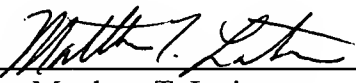
For the reasons presented above and in the previous response, Applicants respectfully submit that claims 1 and 28 are patentable over the combination of Brange, Markussen *et al.*, and Brange *et al.* Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. § 103(a), and allowance of claims 1 and 28.

Applicants respectfully submit that, upon indication of allowable subject matter in generic claim 1, the Office is required to examine claims directed to non-elected species, as set out in the Election of Species Requirement dated June 29, 1999. MPEP § 809.02(c).

If the Examiner believes anything further is necessary to place this application in better form for allowance, she is invited to contact Applicants' undersigned representative at the telephone number or e-mail address listed below. Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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